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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,856	09/11/2003	Eszter Birck-Wilson	G0744.70028US01	5220

31904 7590 05/01/2008

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

MAIL DATE	DELIVERY MODE
05/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,856	BIRCK-WILSON ET AL.	
	Examiner	Art Unit	
	JAMES L. GRUN	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007 and 16 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,31-44,57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,31-44,57 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The amendment filed 16 January 2008 is acknowledged and has been entered. Claims 22-30, 45-56, 58, and 62 have been cancelled. Claims 1-21, 31-44, 57, and 59-61 remain in the case. Claims 57 and 59-61 have been withdrawn from further consideration as being drawn to a non-elected species, there being no allowable generic or linking claim.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 1-21, 31-44, 57, and 59-61 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons of record as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly the invention commensurate in scope with these claims. As set forth, one would not readily envision any starting samples for use other than those containing IgG4 absent further guidance and unpredictable experimentation. As also set forth, unguided, random, unpredictable experimentation to determine functional conditions for IgG4 half and whole antibody separation other than those taught in the specification is undue.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

Applicant urges that the examiner's argument is mere allegation regarding differences between IgG4 and other non-IgG4 immunoglobulins in forming the relevant mixtures. This is not found persuasive for the reasons of record. As set forth, one would not readily envision any starting samples for use other than those containing IgG4 because applicant provides no guidance to samples containing any other mixtures of half and whole antibodies amenable to use in the instant method other than to those containing IgG4 and because, as set forth in the evidence provided in the cited publications, other immunoglobulin isotypes are not known to predictably produce such mixtures. Notwithstanding applicant's assertions to the contrary, the issue is not whether non-IgG4 immunoglobulins could possibly form mixtures of half and whole molecules in some undisclosed manner, the issue is if applicant has provided sufficient guidance to how one predictably obtains starting sample mixtures to practice the method other than with those containing IgG4.

Applicant also urges that the suggestion in the specification to use hydrophobic columns enables their use because separation of proteins with hydrophobic interaction columns is within the skill of one in the art. This is not found persuasive for the reasons of record that applicant has not provided sufficient guidance for conditions which predictably function for separation even of IgG4 half and whole antibodies, other than with a cation exchange column, and one would not be assured of the ability to predictably separate the mixtures absent further experimentation, unguided by applicant's specification as to other predictable functional columns and conditions. Notwithstanding applicant's assertions to the contrary, applicant's

suggestions to try separation means, other than those specifically exemplified, with other conditions known generally to separate protein mixtures provides a mere suggestion to one in the art to perform further random unpredictable experimentation to determine with which means and conditions one could achieve the desired goal of separation and does not guide one to particular combinations of columns and conditions that are functional for the separation. Such an invitation to experiment does not provide an indication that applicant had possession of the invention of the scope as claimed at the time the application was filed and does not provide an enabling disclosure.

Again, with regard to the arguments above, as the court stated in the decision of *Genentech Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (CAFC 1997), "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 10, 12-15, 20, and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by King et al. (Biochem. J. 281: 317, 1992) in light of Colcher et al. (Cancer Res. 49:

1738, 1989) and either of Schuurman et al. (Molecular Immunol. 38: 1, 2001) or the instant disclosure for reasons of record.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

Applicant urges that King et al. do not teach separation of half and whole immunoglobulin molecules. This is not found persuasive for the reasons of record because the reference clearly teaches that the half and whole molecules were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis, including with a rod (i.e. columnar) gel, which inherently retains both half and whole molecules and differentially retards mobility. Notwithstanding applicant's allegations to the contrary, the examiner did not concede that King et al. did not separate half and whole molecules, the examiner set forth that the reference "did not separate the molecules other than by sodium dodecyl sulfate polyacrylamide gel electrophoresis, including with a rod (i.e. columnar) gel." Notwithstanding applicant's assertions to the contrary, the reference teaches, in light of Colcher et al., storage of the chimeric immunoglobulin after ion exchange chromatography in phosphate buffered saline (having a pH of 7.4, see King et al., page 318, col. 1), and then exposing the mixture to a reduced pH solution that dissociates immunoglobulin molecules comprised of two half molecules, i.e. the SDS/PAGE buffer (of pH 6.8 (see e.g. Fig. 4)) (pages 319-320).

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

Claims 1, 2, 5, 8, 9, 12, and 20 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Palmer et al. (Biochem. 3: 863, 1964) for reasons of record.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive. Applicant urges that a reduced pH was part of the reduction protocol in Palmer et al. and that the reference does not teach a further reduction in pH to dissociate associated half molecules of immunoglobulin. This is not found persuasive for the reasons of record. The reduction was performed at pH 5.0 and the "pH was adjusted to 2.4 . . . to determine the extent of dissociation into half-molecules" (see e.g. page 865, col. 2), specifically prior to a column separation to separate a mixture of half and whole molecules (see e.g. Fig. 3), because reduction did no go to completion with different reduction conditions (see e.g. pages 865-867, including Figs. 1-3) and the half-molecules are known to be re-associated at higher, such as neutral, pH (see e.g. page 863).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-5, 8-21, and 31-42 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over the combined teachings of King et al. (Biochem. J. 281: 317, 1992), Schuurman et al. (Molecular Immunol. 38: 1, 2001), Angal et al. (Mol. Immunol. 30: 105, 1993), and Palmer et al. (Biochem. 3: 863, 1964) for reasons of record.

Applicant's arguments filed 16 January 2008 have been fully considered but they are not deemed to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this regard, applicant urges that King et al., Schuurman et al., or Palmer et al., individually, do not teach reduction in pH to dissociate associated half-molecules of immunoglobulin in a mixture with whole immunoglobulin molecules. This is not found persuasive for the reasons of record, particularly with regard to the teachings of Schuurman et al. and Palmer et al. wherein a reduction in pH is directly suggested for the dissociation of non-covalently associated antibodies, specifically prior to a column separation (Palmer et al.). In this regard, the argument is not found persuasive in view of the teachings of Palmer et al. set forth above and incorporated herein.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR REPLY TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE MAILING DATE OF THIS ACTION. IN THE EVENT A FIRST REPLY IS FILED WITHIN **TWO MONTHS** OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE **THREE-MONTH** SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR REPLY EXPIRE LATER THAN **SIX MONTHS** FROM THE MAILING DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
April 30, 2008

/Christopher L. Chin/

Primary Examiner, Art Unit 1641